REMARKS

Amendments

Claims 1-5, 7, 9-15, 22 and 25-28 have been canceled, and claims 6, 8, 30, 31 and 33-35 have been amended. Upon entry of the amendment, claims 6, 8, 16-21, 23, 24 and 29-35 will be pending. Support for the added claims can be found in the specification, for example, on page 7, lines 18-22; page 18, lines 24 through page 19, line 28; Example 2; the Figures; and in the claims as originally filed.

The specification has been amended to update cited application information. Previously cited U.S. Patent Application Ser. No. 08/971,310, filed November 17, 1997 (and now abandoned) was converted to 60/684,194, on which issued US patent no. 6,815,185 depends as a priority application filing. Contrary to the Examiner's assertions, the amendment does not recite new matter as the only document incorporated by reference is the disclosure of the originally cited 08/971,310 application. US patent no. 6,815,185 is only being cited as a publicly available document which contains the disclosure of the '310 application.

Rejections

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 6, 8, 16-21, 23 and 24 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility for the reasons of record.

Applicant does not agree. Amended claim 6 is drawn to a transgenic mouse whose genome comprises a null endogenous KIR5.1 allele.

1. The Utility Requirement

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

. . .

> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. The present invention satisfies either standard.

The standard for "credible" is defined as:

> . . . whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

(MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office's own guidance to Examiners:

> *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. [citations omitted] . . . Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false.
>
> Compliance with 35 U.S.C. 101 is a question of fact [citations omitted]. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. . . . To do this, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art.

(MPEP 2107.02, III(A)(emphasis added).

> **Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts.** Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the

effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

(MPEP 2107.02, III(B)(emphasis in original and added). The Guidelines additionally provide that:

> There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).

(MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. An assertion of utility is presumed to be true. The burden is on the Examiner to show that one of ordinary skill would find the asserted utility to be false. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
>
> . . .

> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834)(emphasis added)(copy attached). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

> Now that the human and mouse genome sequences are known, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (Mus musculus) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
>
> . . .
>
> A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

With respect to claims drawn to transgenic mice having a null allele, the following comments from Austin are relevant:

> **Null-reporter alleles should be created**
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(p. 922)(emphasis in original, emphasis added).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function), one that is clearly recognized by those skilled in the art.

For example, according to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) (copy of relevant pages attached), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has

either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.

(p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached), another well respected textbook in the field of genetics:

The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.

(p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.

(preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000)(copy of relevant pages attached):

The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.

(p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.

Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.

(p. 1, rear cover)(emphasis added).

2. Well-Established Utility

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Applicant submits that in light of arguments of record, a person of ordinary skill in the art would immediately appreciate why the invention is useful. Thus, it cannot be reasonably debated that a person of ordinary skill in the art would not immediately appreciate why the invention is useful: for determining gene function.

3. Substantial Utility

The Examiner argues that the asserted utilities are not substantial (p. 4).

According to the MPEP:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;
>
> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

(MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

> Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). Thus, the cited portions of the MPEP guidelines relate to the situation where further research is required to establish or confirm any utility. Such is not the case here. Knockout mice have a well-known use in the study of gene function. In the present case, the present invention does not require further research to establish a utility. Applicant has provided an *in vivo* model for studying the function of the KIR5.1 gene. Applicant has also determined that the gene is associated with, for example, dwarfism, decreased body weight, decreased spleen weight and decreased spleen weight: body weight ratio. The Applicant has provided an immediate benefit to the public. Whether additional research is required to identify drugs capable of targeting the gene is irrelevant to whether the claimed invention has satisfied the utility requirement.

Commercial use and acceptance is an important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. The claimed mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase. This database has been subscribed to by at least three of the world's largest pharmaceutical companies, Merck, Pfizer and GSK. In addition, at least one (1) large pharmaceutical company has ordered the presently claimed mouse. This acceptance more than satisfies the practical utility requirement of section 101 as **it cannot be reasonably argued that a claimed invention which is actually being used by those skilled in the art has no "real world" use**. (see, for example, Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065, 1104 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1980)("lack of practical utility cannot co-exist with infringement and commercial success);

(Lipscomb's Walker on Patents, §5:17, p. 562 (1984)("Utility may be evidenced by sales and commercial demand.")

As evidence of such sales and purpose of such use, attached hereto is a Rule 132 Declaration from Robert Driscoll, Vice President of Intellectual Property & Legal Affairs of Assignee, Deltagen.

4. Specific Utility

The Examiner states that the asserted uses are not specific because "the phenotype is not specific to the knocked out gene" (p. 6); and "any mouse could be used" (p. 9).

Applicant does not agree. "All knockout mice" cannot be used to study the function of the KIR5.1 gene. The use of each knockout mouse is specific to the particular gene which is disrupted.

According to the MPEP, "specific utility" means "specific" to the subject matter claimed as compared to a "general utility" that would be applicable to the broad class of the invention (MPEP 2107.01). Use of the KIR5.1 -/- mouse to study the function of the KIR5.1 gene and the association of the KIR5.1 gene with, for example, anxiety and growth disorders, is specific to this mouse. Even if there were many other genes associated with these abnormalities, only a KIR5.1 knockout mouse (as opposed to all other knockout mice) would be used to study the specific role of this gene in these conditions. The Examiner is respectfully requested to explain (1) how the asserted utility of characterizing the function of the KIR5.1 gene would be applicable to all other knockout mice; and (2) how the asserted use of studying the association of the KIR5.1 gene with anxiety and growth disorders would be applicable to all other knockout mice. The Examiner is requested to explain how all other knockout mice would be used to study the function of the KIR5.1 gene.

Applicant submits that by arguing that "any mouse could be used," the Examiner is confusing "specific" with "unique."

In addition, the mice within the scope of claim 33 contain a *lacZ* gene. Their use in studying gene expression is clearly recognized by those skilled in the art:

> **Null-reporter alleles should be created**
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point

> for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 922)(emphasis in original; emphasis added)(copy attached). As cited in Austin, and as is well known by one of ordinary skill, the purpose of expression analysis is to determine where the gene is expressed.

The Examiner argues that the specification does not teach what promoter is driving the *lacZ* gene.

As is well understood in the art, the *lacZ* gene is inserted into the endogenous gene. In this case, the *lacZ* gene was inserted into the locus of the KIR5.1 gene. Expression is driven by the endogenous promoter. Expression of the *lacZ* gene indicates where the KIR5.1 gene is expressed. This use is specific for this mouse – knockout mice in general cannot be used for this purpose. The Examiner is respectfully requested to explain how all other knockout mice would be used to study expression of the KIR5.1 gene.

5. In re Brana

The Examiner argues that none of the asserted utilities are credible, arguing, for example, that the specification does not disclose a specific human disease associated with the phenotype (page 6).

The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proffered by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and

therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, *citing In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly,

the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. As discussed above, the claimed mice have demonstrated specific phenotypes. The acceptance among those of skill in the art of knockout mice demonstrating such properties is clearly demonstrated.

Definitive proof that the phenotypes observed in the null mouse would be the same as those observed in humans is not a prerequisite to satisfying the utility requirement. It is enough that the claimed mouse demonstrates phenotypes, relative to a wild type control mouse, and that knockout mice are recognized in the art as models for determining gene function, both in mice and in humans. According to Austin et al.:

> Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.

(p. 921)(emphasis added).

In addition, as pointed out by Doetschman, one clearly skilled in the art, (*Laboratory Animal Science* 49:137-143, 137 (1999)(copy attached), the phenotypes observed in mice do correlate to gene function:

> The conclusions will be that the knockout phenotypes do, in fact, provide accurate information concerning gene function, that we should let the unexpected phenotypes lead us to the specific cell, tissue, organ culture, and whole animal experiments that are relevant to the function of the genes in question, and that the absence of phenotype indicates that we have not discovered where or how to look for a phenotype.

(emphasis added).

In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated – as the Court determined that the murine tumor model represented a specific disease. Here, the invention relates to a disruption of a murine gene in a mouse. The claimed mouse demonstrates, for example, abnormal stimulus processing and growth abnormalities – like the tumor mouse

model, any one of which would be recognized as a specific disease. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied the initial burden.

6. Additional Examiner Arguments

The Examiner argues that the claimed mice do not provide a "definitive answer on the function of the Kir5.1 gene" (page 4).

Applicant is not claiming the Kir5.1 gene. Applicant is claiming a mouse having a null Kir5.1 gene. Moreover, contrary to Examiner's assertion, an absolute correlation is not required for patentability purposes, only a reasonable one. As held by the CCPA: "Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty." (Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)). As cited above, phenotypes observed in mice do correlate to gene function (Doetschman, *Laboratory Animal Science* 49:137-143, 137 (1999)).

The Examiner cites Bowery for the proposition that knockout mice do not have a well-established utility for determining gene function because knockout mice do not necessarily reveal the function of the knocked out gene (page 5).

Bowery is clearly unsupportive of the Examiner's position. For example, Bowery discusses use of hot-plate, tail-flick and paw pressure protocols to evaluate acute pain behavior in GABA-B1 null mutant mice. Based on the reported data, Bowery concludes "it is likely that GABA-B-mediated effects do indeed exert a tonic control of nociceptive proceses in the naïve animal" (p. 255, col.2). Thus, Bowery supports the utility of knockout mice in evaluating the role of GABA genes.

The Examiner cites Olsen for the proposition that the phenotype of the knockout mice "may" be a result of other genes compensating for the loss of the protein.

First, the Examiner's argument is based on conjecture, not fact. Second, even if true, whether Kir5.1 directly or indirectly causes these phenotypes is irrelevant – a drug targeting the gene would have the same effect – directly or indirectly.

Third, Olsen is clearly unsupportive of the Examiner's position that such knockout mice have do not have a well-established utility. Olsen states that "gene targeting is useful in delineating the contribution of a given gene product to phenotypic characteristics" even though "some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype" (emphasis added). In fact, even with respect to GABA genes, Olsen concludes that "the use of mutant and knockout mice has aided understanding of the roles of GAD and GABAR in the intact mammalian organism, with much promise for additional information to come" (Olsen at 91). Even with respect to mice having increased lethality, Olsen states: "[t]he γ2 and β3 subunit knockouts are associated with early postnatal lethality but have nonetheless provided considerable new information about their importance, include relevance to neurodevelopment, synaptogenesis, and possibly human disease. The β3 is a strong candidate for involvement in the epilepsy and other phenotypic attributes of Angelman syndrome, a human genetic disorder characterized by mental retardation, seizures, motor incoordination, and sleep disturbances. The γ2L knockout has allowed direct testing and negation of the selective subunit hypothesis for ethanol modulation of GABAR function. The δ subunit knockout appears to provide information about the function of GABAR in adult cerebellum, dentate gyrus of the hippocampal formation, and the thalamus. GAD_{65}, GABAR β3, and GABAR δ subunit knockouts all exhibit spontaneous seizures, but of different sorts, confirming suspicions that GABAR malfunction might produce epilepsy by more than one mechanism and providing excellent animals models for investigation of the cause of the seizure phenotype." (Olsen at 91-2).

Olsen goes further: "[i]n summary, transgenic and knockout mice have demonstrated that GABA plays a major role in brain development, control of palate formation, and epileptogenesis via multiple mechanisms." (Olsen at 92). It is untenable to cite Olsen as standing for the proposition that knockout mice do not have a well accepted use.

In the present case, the claimed Kir5.1 null mouse in fact demonstrate phenotypes. Olsen would agree that such mice are clearly useful.

The Examiner argues that background and genetic factors may have an effect on phenotype, citing Bullock and Paylor (pp. 7-8).

The specification and claims clearly recite the phenotypes were observed by comparing the claimed mice with wild-type control mice. It is well known in the art to compare the transgenic mice with controls of the same background. Whether background has an effect on

phenotype is irrelevant where the observed phenotypes are compared with mice of identical background. Attached hereto is a Declaration from John Burke, Attorney of Record, stating that the transgenic mice were in fact compared with controls of identical background.

The Applicant notes that the Examiner has not cited any evidence that background affects non-behavioral phenotypes such as the recited growth disorders. For example, no argument has been made that background affects "dwarfism." The Applicant reminds the Examiner that a claimed invention need only have a use to satisfy the utility requirement.

The Examiner argues that a mouse with increased PPI as claimed does not correlate to schizophrenia; that abnormal prepulse inhibition is not specifically treated in humans; and that prepulse inhibition is a measure of disease and not a model of disease (pp. 8-10).

The Examiner is requested to point out where the claims recite increased PPI or otherwise reference PPI.

With regard to Austin and the NIH citation, the Examiner argues that the references were published well after the present application was filed.

The Examiner cites no legal support why Austin and the NIH should not be considered. The references are not being cited to support a post-filing assertion of utility. The goal of determining gene function is clearly set forth in the specification. Austin supports this statement. Moreover, courts have accepted post-filing activities to support an asserted utility. For example, in *In re Brana*, the application's filing date was June 30, 1988. The applicants relied on an affidavit submitted June 19, 1991 to provide evidence of the compounds activity, *a date well after the filing date*. The Federal Circuit noted:

> Enablement, or utility, is determined as of the application filing date [citations omitted]. The Kluge declaration, though dated after applicants filing date, can be used to substantiate any doubts as the asserted utility since this pertains to the accuracy of a statement already in the specification. [citations omitted] It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

(*Brana*, n.19). Thus, Austin and the NIH citation should have been considered by the Examiner as evidence supporting the utility of the claimed invention.

As noted by the Examiner, Austin states knockout mice "can" be used to elucidate gene function. Therefore, the asserted use is credible.

The Examiner cites *Schoenwald* for the proposition that providing evidence that a product was known in the art was not evidence that the product had patentable utility (p. 14).

Schoenwald does not stand for the proposition cited by the Examiner. In fact, the utility requirement was not at issue. The case involved the novelty of a claimed composition that was described in a prior art reference. The court held that the reference need not recite a utility in order to anticipate the claimed composition.

6. Summary

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying KIR5.1 gene function with respect to the cited phenotypes, for studying gene expression, and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

An assertion of utility is credible unless the logic underlying the assertion is seriously flawed, or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (MPEP 2107.02, III(B)). The Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered false by a person skilled in the art (MPEP 2107.02, III(A)). The Examiner has failed to provide any facts or reasoning sufficient to establish that a person of ordinary skill would not believe Applicant's assertion of utility.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly made a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific and substantial. (*In re Brana*; MPEP § 2107).

Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 6, 8, 16-21, 23, 24 and 29-35 have been rejected for lack of enablement, as the claimed invention allegedly lacks utility. As set forth above, it the Applicant's position the claimed invention satisfies the utility requirement and therefore one skilled in the art would clearly know how to use the invention.

The Examiner argues that the claims are not enabled because the specification does not enable using a transgenic with a wild-type phenotype.

The enablement requirement is determined based on the claimed invention: a transgenic mouse having a null Kir5.1 allele. There is no requirement, and the Examiner has not cited any, that a claim to a composition of matter recite properties of that composition. The phenotypes of the claimed invention, a transgenic mouse having a null KIR5.1 allele, are inherent to the mouse. The specification fully enables the making and using of such a mouse.

With regard to claims 16 and 17, the specification clearly describes how one skilled in the art would test the claimed mice to observe startle response and stimulus processing disorder. Therefore, the claims are enabled.

Withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 112, 1st paragraph

Claim 6, 8, 16-21, 23, 24 and 29-35 stand rejected as allegedly failing to comply with the written description requirement.

The Examiner argues that "null Kir5.1 allele" is new matter.

Applicant disagrees. According to the Federal Circuit:

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language.

In re Kaslow, 707 F.2d 1366, 217 USPQ 1089 (Fed.Cir.1983). The Applicants were clearly in possession of a mouse with a null Kir5.1 allele. According to the specification, a "transgenic animal" is an animal that contains within its genome a specific gene that has been disrupted or otherwise modified or mutated by the method of gene targeting. "Transgenic animal" includes both the heterozygous animal (*i.e.*, one defective allele and one wild-type allele) and the homozygous animal (*i.e.*, two defective alleles). The term "null" is well understood in the art as meaning ablating the function of that allele. For example, according to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached):

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can

generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.

(p. 508)(emphasis added). Applicant submits that the written description requirement is clearly satisfied.

The Examiner argues that the phrase "comprising exogenous DNA" is new matter.

Applicant does not agree. However, the phrase has been deleted rendering the rejection moot.

The Examiner argues that the phrase "increased startle response is an indication of increased level of anxiety" in claim 17 is new matter.

The phrase finds support on page 55, lines 8-11 of the specification.

The Examiner argues that "selection marker" is new matter.

Applicant does not agree. However, the phrase has been changed to selectable marker.

The Examiner argues that "visual marker" is new matter.

Applicant does not agree. However, the phrase has been deleted.

Withdrawal of the rejections is requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 6, 8, 16-21, 23, 24 and 29-35 stand rejected as allegedly indefinite.

The Examiner asserts that the "metes and bounds of 'Kir5.1 allele' in claim 6 is indefinite."

The definition cited by the Examiner (page 7, lines 1-4 of the specification) is a non-species specific definition of the Kir5.1 gene, and therefore would include homologs and orthologs of SEQ ID NO:1. However, in the context of the present claim; a transgenic mouse having a null endogenous Kir5.1 allele, it would be clearly understood by one skilled in the art that the term refers to the mouse Kir5.1 allele.

The Examiner asserts the term "null" in the context of the allele is indefinite. Applicant disagrees.

In proper context, the claim encompasses a "transgenic mouse whose genome comprises a null Kir5.1 allele." The specification provides that "[t]ransgenic animal" refers to an animal that contains within its genome a specific gene that has been disrupted or otherwise modified or mutated by the method of gene targeting. "Transgenic animal" includes both the heterozygous

animal (*i.e.*, one defective allele and one wild-type allele) and the homozygous animal (*i.e.*, two defective alleles)." (pages 6-7). "In a preferred embodiment, the disruption is a null disruption, wherein there is no significant expression of the Kir5.1 gene." (page 7). It is clear from the claim that one or both alleles have been disrupted. Thus, the claim encompasses both heterozygous and homozygous transgenic mice.

The term "null" is well understood in the art as meaning ablating the function of that allele. For example,

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached):

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.

(p. 508)(emphasis added).

According to Hasty (*Gene Targeting, Principles, and Practice in Mammalian Cells* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

> Since the most common experimental strategy is to ablate the function of a target gene (null allele) by introducing a selectable marker gene . . .

(page 1)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

> Knockout mice have a gene deleted. The null mutant homozygous knockout mouse is deficient in both alleles of a gene, the heterozygote is deficient in one of its two alleles for the gene. The genotype is -/- for the null mutant, +/- for the heterozygote, and +/+ for the wildtype normal control.

(p. 2)(emphasis in original).

As the term "null allele" is clearly recognized in the art, the claim satisfies the definiteness requirement.

The Examiner argues that the phrase "wherein the increased startle response is an indication of increased level of anxiety" is unclear.

Applicant does not agree. The startle test is designed to test the level of anxiety. The test results show that the claimed mice demonstrated an increased level of anxiety as compared to the control mice.

The Examiner argues that the term "dwarfism" is unclear.

Applicant does not agree. According to Merriam Webster dictionary, the term means "the condition of stunted growth." One skilled in the art would clearly understand the meaning of the term dwarfism.

The Examiner argues that the term "growth abnormality" is subjective and therefore unclear.

Applicant does not agree. Claim 19 reads: "wherein the transgenic mouse exhibits, relative to a wild-type control mouse, a growth disorder comprising at least one of the following phenotypes: dwarfism, decreased body weight, decreased spleen weight and decreased spleen weight: body weight ratio." Thus, not only is the growth disorder defined relative to a wild-type control mouse, but the disorder comprises 1 of 4 specifically defined phenotypes. Applicant submits that the term would be clearly understood by one skilled in the art.

Claims 29-35 have been amended to recited dependency on claim 6.

Applicant respectfully requests withdrawal of the rejections.

Rejection under 35 U.S.C. § 102(b)

The claims had been previously rejected as being anticipated by Signorini, which is cited as disclosing a mouse having a disrupted Kir3.2 gene. The Examiner argues that the Kir3.2 gene "is a Kir5.1 allele" because it shares homology with SEQ ID NO:1.

Applicant does not agree. As argued above, one skilled in the art would understand the term "endogenous Kir5.1 allele" as used in claim 6 to mean the mouse Kir5.1 allele which encodes cDNA comprising SEQ ID NO:1. Signorini discloses a mouse having a disrupted GIRK2 gene. One skilled in the art would not agree with the Examiner that the GIRK2 gene is a Kir5.1 allele. Signorini does not disclose the claimed mouse: a transgenic mouse having a null endogenous Kir5.1 allele, and therefore does not anticipate the claimed invention. Withdrawal is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 6, 8, 16-18, 29-33 and 35 stand rejected as allegedly being obvious over Signorini in view of Mouri, which is cited as disclosing SEQ ID NO:1. Signorini discloses a mouse having a disrupted GIRK2 gene. The Examiner argues that it would have been obvious to substitute the sequence disrupted by Signorini with SEQ ID NO:1 to "gain clues" regarding the function of the Kir5.1 allele.

Applicant respectfully traverses the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Applicant respectfully submits that the Office Action fails to establish a prima facie case of obviousness because there is no reasonable expectation of success to that which Applicant has done by modifying the cited references. Moreover, Applicant respectfully submits that the combination of the references fails to teach or suggest all the claimed subject matter.

As a preliminary matter, Applicant questions how the Examiner can argue that the requisite motivation exists to create the claimed subject matter, when the Examiner argues above that the claimed subject matter has no patentable utility and that one skilled in the art would not know how to use the claimed subject matter.

The cited references, neither alone or in combination, teach or suggest the presently claimed subject matter. There is no suggestion in either reference that one should substitute the disrupted GIRK2 gene with the Kir5.1 allele.

Applicant submits that the cited references are not enabling or operative to produce the claimed transgenic mouse because neither reference teaches or suggests the claimed invention. Signorini requires cloning of the GIRK2 gene, knowledge of the genomic sequence and restriction mapping of the targeted gene to produce a targeting construct and the GIRK2 transgenic mice (see Signorini, Materials and Methods). SEQ ID NO: 1 is a cDNA. As the Examiner is aware, cDNA includes only the coding aspects of the gene. Mouri provides nothing more than an Accession number without any disclosure. Without a teaching of the genomic sequence or restriction mapping of the Kir5.1 gene, one of ordinary skill in the art would not be

able to do that which Applicant has done, and therefore would not have a reasonable expectation of success in making the claimed transgenic mouse.

Moreover, Applicant submits that the combination of cited references fails to teach or suggest each and every limitation of the claimed invention. Signorini teaches a mouse having a disrupted GIRK2 gene, not the Kir5.1 gene (Applicant questions whether Signorini provides an enabling disclosure as to how to create any targeting vector). Mouri teaches the cDNA of the Kir5.1 gene. Neither reference teaches or suggests the claimed invention: a mouse having a null Kir5.1 allele. Therefore, the claimed invention would not have been obvious.

Applicant respectfully requests the rejection be withdrawn.

In view of the above amendments and remarks, Applicant respectfully requests reconsideration and a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.

Respectfully submitted,

7-6-05

Date

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